PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference JWJ01124WO	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/GB2004/003117	International filing date *(day/month/year)* 16.07.2004	Priority date *(day/month/year)* 18.07.2003
International Patent Classification (IPC) or national classification and IPC A61N1/40, A61K41/00		
Applicant OXFORD INSTRUMENTS SUPERCONDUCTIVITY LIMITED ET AL		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 8 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18.01.2005	14.09.2005
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Petter, E Telephone No. +31 70 340-2866

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003117

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-23	as originally filed
Claims, Numbers	
1-41	as originally filed
Drawings, Sheets	
1/10-10/10	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/003117

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,8,10,11,20-28,31,34,37,38
	No:	Claims	1-6,9,13-19,29,30,32,33,35,36,39-41
Inventive step (IS)	Yes:	Claims	12
	No:	Claims	1-11,13-41
Industrial applicability (IA)	Yes:	Claims	1-41
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V.

1 The following documents are referred to in this communication:

D1 : WO 01/17611 A (EUROP I OF SCIENCE AB ;FREDRIKSSON SARAH (SE); KRIZ DARIO (SE)) 15 March 2001 (2001-03-15)

D2 : US 6 231 496 B1 (WILK PETER J ET AL) 15 May 2001 (2001-05-15)

D3 : HALBREICH A ET AL: "Damage to the protein synthesizing apparatus in mouse liver in vivo by magnetocytolysis in the presence of hepatospecific magnetic nanoparticles" JOURNAL OF MAGNETISM AND MAGNETIC MATERIALS, ELSEVIER, AMSTERDAM, NL, vol. 248, no. 2, July 2002 (2002-07), pages 276-285, XP004371011 ISSN: 0304-8853

D4: JORDAN A ET AL: "MAGNETIC FLUID HYPERTHERMIA (MFH)" SCIENTIFIC AND CLINICAL APPLICATIONS OF MAGNETIC CARRIERS, XX, XX, 1997, pages 569-595, XP000858786

2.1 Document **D1** discloses (the references in parenthesis applying to this document):

the use of one or more magnetic particles in the manufacture of a medicament for administration to a patient to treat a disorder associated with a cellular or tissue structure, or the accumulation of an undesirable biological material wherein the or each particle is intended to localise at or within the structure or material (see page 3, lines 3-21), and

wherein the treatment is intended to be carried out by applying a magnetic field, to induce the or each particle to rotate, to thereby disrupt the structure or material (page 4, lines 15-35);

wherein the or each magnetic particle has intrinsic magnetization, said magnetization being stabilised by inherent magnetocrystalline anisotropy and/or by shape anisotropy (page 4, lines 12-15);

Further explanations:

concerning the rotation of the particle:

When magnetic particles are subjected to an alternating magnetic field, as it is the case in **D1** (page 4, lines 17-18), the magnetization within the particles changes under the influence of said magnetic field, which causes the well known hysteresis loss that generates heat (**D1**: page 5, lines 23-28). It is clear however that the change of magnetization does not appear suddenly but the movement of the domain walls takes some time which is reflected in the hysteresis curve. Therefore, as long as the magnetization (magnetic moment) and the external magnetic field are not yet aligned, the particle will experience a torque according to the formula at the bottom of page 6 of the Application. Whether the particle actually rotates depends on the moment of inertia (see for further explanation document **D4**: page 576, first paragraph and page 578, first paragraph). Since the particles in **D1** are small nanoparticles (size of 0.1-300 nm), it is believed that the moment of inertia of the particles in **D1** is small enough to allow some mechanical rotation of the particle.

Furthermore, in an alternate embodiment of **D1**, "mechanical directional vibrations" (see **D1**: page 5, lines 29-30) are caused by overlapping magnetic fields of different frequencies (see page 6, lines 15-21). In this case, the vector **F** of the translational force (see Application page 7, second formula) does not make a simple "back and forward" movement but instead rotates.

concerning the intrinsic magnetization

Any "magnetic particle" is considered to have at least to a certain extent an intrinsic magnetization, i.e. remanent magnetization. This is clearly also the case in **D1**, see page 4: lines 12-15: "Without...the external magnetic field...the dipoles".

Even if the particles in D1 are metal oxide which is considered a soft magnetic material as such, because of their small size (0.1 -300 nm) they will be single domain or pseudo single domain. As the Application explains (figure 2), such small particles generally have a higher coercitivy and higher remanent magnetization than would be expected with respect to their material property.

Therefore, document **D1** discloses in combination all the features defined in independent claim 1. Hence the subject-matter of this claim is not new (Article 33(2) PCT).

2.2 Furthermore, the additional features of dependent claims 2-11 are either present in **D1** or provide straightforward modifications that come within the scope of the customary practice followed by persons skilled in the art:

- Claims 2, 3: mammalian cells, tumour are disclosed in D1: page 3, lines 12-21.

- Claims 4-6, 9: antibody coating is also disclosed in D1: page 3, line 5.

- Claims 7-8 recite some well known magnetic materials.

- The size ranges defined in claims 10-11 largely overlap with the size range defined in **D1**: page 3, lines 5-6.

Therefore, dependent claims 2-11 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT). The subject matter of dependent claim 12, however, does not appear to be disclosed or suggested by the available prior art.

3.1 Method claim 13 basically defines the same technical features as claim 1. The applied magnetic field direction and/or amplitude in **D1** is also varied over time (see **D1**: page 4, lines 18-20). The lack of novelty objection raised under point 2.1 therefore also applies to claim 13 (Article 33(2) PCT).

3.2 Furthermore, the additional features of dependent claims 14-28 are either present in D1 or appear to provide straightforward modifications that come within the scope of the customary practice followed by persons skilled in the art:

- Claims 14-18: biological material, cellular tissue, mammalian cells, and a tumor as the material to be disrupted are all disclosed in **D1**: page 3, lines 12-21.

- Claim 19: the particles of claim 4 are also disclosed in **D1**: page 3, lines 3-6.

- Claims 20-27 appear to recite some straightforward options concerning the configuration of the alternating magnetic field.

- Claim 28: MR imaging in combination with the disruption of cells (magnetocytolysis) is already known from **D3** (see page 284, last five lines of second column)

4.1 The magnetic field generator defined in indepedent claim 29 for use in the method of claims 1 and 13 respectively, is also disclosed in **D1** (see figure 3 and page 5, line 31 - page 6, line 25). Therefore, the subject matter of claim 29 also lacks novelty over **D1** (Article 33(2) PCT).

4.2 Furthermore, the additional features of dependent claims 30-38 are either present in **D1** or provide straightforward modifications that come within the scope of the customary practice followed by persons skilled in the art. Therefore, dependent claims 30-38 do not appear to contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step (Article 33(2) and (3) PCT).

5.1 The magnetic particle as referred to in claim 4 is known from **D1** (see page 3, lines 3-6). Therefore, the subject matter of claim 39 also lacks novelty over **D1** (Article 33(2) PCT).

5.2 D1 also discloses a composition comprising a plurality of particles. Such particles can only be administered to a patient in a pharmaceutically acceptable buffer, which is therefore considered implicitely disclosed in **D1**. The use of the composition in **D1** is therapeutic (page 3, lines 19-21). Hence, the subject matter of claims 40-41 is also anticipated by **D1** (Article 33(2) PCT).

6. Document **D2** also discloses the subject matter of at least independent claim 1 since the magnetic particles in **D2** are also rotated (see column 1; lines 61-65: "orient the particles" i.e. rotate them) and thereby disrupting the uterine lining (see column 5, lines 53-59: the additional microwave radiation for heating is merely optional). Note that claim 1 does not specify that the particles should rotate continously, the initial

rotation (orientation) of the particles in **D2** once the magnet is applied is considered sufficient to anticipate the subject matter of claim 1 (Article 33(2) PCT).

Re Item VIII
Certain observations on the international application

1. Claims 19 and 39-41 include a reference to dependent claims 4-12, which are of another category. It is therefore not clear whether this reference includes, or not features of the particle as defined in independent claim 1.